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FILING DATE: *March 18, 2004*

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Certifying Officer

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)			
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)	
Ryuji UENO		Potomac	Maryland
Ryu HIRATA		Hyogo	Japan
Yasuhiro HARADA		Hyogo	Japan

☐ *Additional inventors are being named on the _____separately numbered sheet(s) attached hereto*

TITLE OF THE INVENTION (500 characters max)

AQUEOUS COMPOSITION COMPRISING THIAZOLE DERIVATIVE

CORRESPONDENCE ADDRESS

Direct all correspondence to the address for SUGHRUE MION, PLLC filed under the Customer Number listed below:

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

ENCLOSED APPLICATION PARTS (*check all that apply*)

Specification

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☐ Drawings — *Number of Sheets* _____ — ☐ Other (specify)

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

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_____

Respectfully submitted,

SIGNATURE Bruce E. Kramer — DATE March 18, 2004

TYPED or PRINTED NAME Bruce E. Kramer — REGISTRATION NO. 33,725

TELEPHONE NO. (202) 293-7060 — DOCKET NO. P80545

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

DESCRIPTION

AQUEOUS COMPOSITION COMPRISING THIAZOLE DERIVATIVE

TECHNICAL FIELD

The present invention relates to an aqueous composition comprising a specific thiazole derivative.

BACKGROUND ART

Vascular adhesion protein-1 (hereinafter to be abbreviated as VAP-1) is an amine oxidase (semicarbazide sensitive amine oxidase, SSAO) which is abundant in human plasma, and shows remarkably increased expression in vascular endothelium and vascular smooth muscle of the inflammatory region. While the physiological role of VAP-1 has not been clarified until recently, VAP-1 gene was cloned in 1998, and VAP-1 has been reported to be a membrane protein that regulates rolling and migration of lymphocyte and NK cell as an adhesion molecule under regulation of expression by inflammatory cytokine. Although the amine to be a substrate is unknown, it is considered to be methylamine generated in any part of living organisms. It is also known that hydrogen peroxide and aldehydes produced due to the amine oxidase activity in the molecule are important factors of adhesion activity.

Thiazole derivatives described the following the formula (A) are useful as VAP-1 inhitor (US provisional application No. 60/442,509, 60/458,369, 60/458,370 and 60/517,377).

$$R^1—NH—X—Y—Z \quad (A)$$

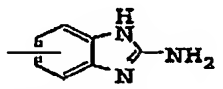
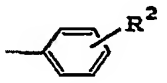
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:

 or 

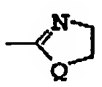
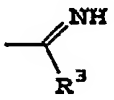
wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$; and

E is optionally protected amino, $-N=CH_2$,

 or 

wherein

Q is -S- or -NH-; and

R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

or a pharmaceutically acceptable salt thereof.

上記チアゾール誘導体の製剤の検討において、特定のチアゾール誘導体を含む水性製剤では、水性製剤で通常使用される塩化ナトリウムの存在により、著しく溶解度が低下し、結晶が析出するため、安定で長期保存可能な水性製剤を得ることができないという問題点があった。

DISCLOSURE OF INVENTION

本発明者は、上記問題点を解決すべく鋭意検討の結果、製剤中に特定の添加剤を配合することにより、特定のチアゾール誘導体の溶解性を保持した安定な水性製剤を得ることを見出し、本発明を完成するに至った。

Thus, the present invention provides the following.

[1] An aqueous composition comprising a compound of the formula (I) [hereinafter sometimes referred to as Compound (I)]:

$$R^1-NH-X-Y-Z \quad (I)$$

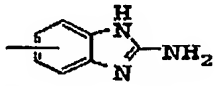
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:

 or 

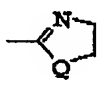
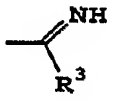
wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$, provided that when B is -CO- or -O-, D is not a bond; and

E is optionally protected amino, $-N=CH_2$,

 or 

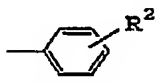
wherein

Q is -S- or -NH-; and

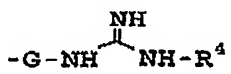
R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

or a pharmaceutically acceptable salt thereof, and an additive selected from the group consisting of polyol, sugar, sugar alcohol, boric acid or its salt, and water.

[2] The composition of [1], wherein Z of the compound (I) is a group of the formula:

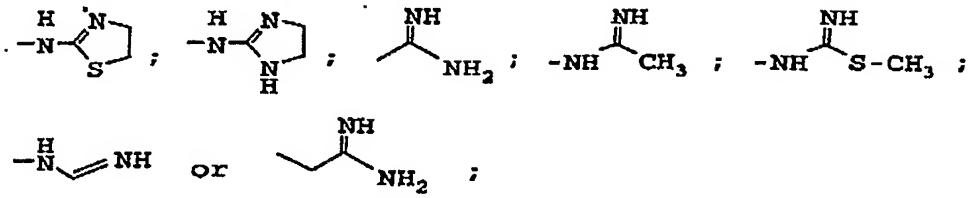


wherein R^2 is a group of the formula:



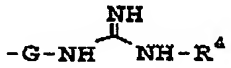
(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is

hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;

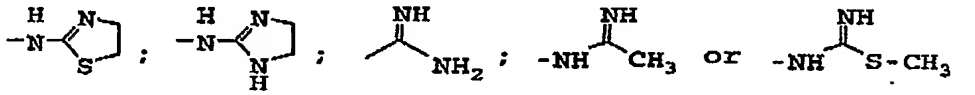


or a pharmaceutically acceptable salt thereof.

[3] The composition of [2], wherein R^2 of the compound (I) is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



or a pharmaceutically acceptable salt thereof.

[4] The composition of any of [1] to [3], wherein R^1 of the compound (I) is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl, or a pharmaceutically acceptable salt thereof.

[5] The composition of [1], wherein the compound (I) is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-

1,3-thiazol-2-yl)acetamide,

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions to be included within the scope of the invention are explained in detail as follows.

Suitable "halogen" includes fluorine, chlorine, bromine and iodine.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" includes straight or branched alkyl having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which more preferred one is C_1-C_4 alkyl.

Suitable "lower alkylthio" includes lower alkylthio containing the above lower alkyl, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, tert-pentylthio and hexylthio.

Suitable "lower alkylene" includes straight or branched alkylene having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, propylene, ethylidene and propylidene, in which more preferred one is C_1-C_4 alkylene.

Suitable "lower alkenylene" includes straight or branched alkenylene having 2 to 6 carbon atom(s), such as -CH=CH-, $-CH_2$-CH=CH-, $-CH_2$-CH=CH-CH_2-, $-CH_2$-CH_2-CH=CH-, -CH=CH-CH=CH-, -CH=CH-CH_2-CH_2-CH_2-, -CH=CH-CH=CH-CH_2-CH_2- and -CH=CH-CH=CH-CH=CH-, in which more preferred one is C_2-C_4 alkenylene.

The above lower alkenylene may be in E or Z form, respectively. Thus, those skilled in the art will recognize that the lower alkenylene includes all E, Z-structures when it has 2 or more double bonds.

Suitable "aryl" includes C_6-C_{10} aryl such as phenyl and naphthyl, in which more preferred one is phenyl. The "aryl" may be substituted by 1 to 3 substituent(s) and the substitution sites are not particularly limited.

Suitable "aralkyl" includes aralkyl wherein the aryl moiety has 6 to 10 carbon atoms [i.e. the aryl moiety is C_6-C_{10} aryl of the above "aryl"] and the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C_1-C_6 alkyl of the above "lower alkyl"], such as benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-phenylpropyl, 4-phenylbutyl and 5-phenylpentyl.

The "optionally protected amino" means that an amino group may be protected with a suitable protecting group according to a method known *per se*, such as the methods described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like. The suitable "protecting group" includes tert-butoxycarbonyl (i.e., Boc), an acyl group as mentioned below, substituted or unsubstituted aryl(lower)alkylidene [e.g., benzylidene, hydroxybenzylidene, etc.], aryl(lower)alkyl such as mono-, di- or triphenyl-(lower)alkyl [e.g., benzyl, phenethyl, benzhydryl, trityl, etc.] and the like.

Suitable "optionally protected amino" includes amino and tert-butoxycarbonylamino (i.e. -NHBoc).

Suitable "heterocycle" includes "aromatic heterocycle" and "non-aromatic heterocycle".

Suitable "aromatic heterocycle" includes 5 to 10-membered aromatic heterocycle containing 1 to 3 heteroatom(s) selected from nitrogen, oxygen and sulfur

atoms besides carbon atom(s), and includes, for example, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyridazine, pyrimidine, pyrazine and the like.

Suitable "non-aromatic heterocycle" includes 5 to 10-membered non-aromatic heterocycle containing 1 to 3 heteroatom(s) selected from nitrogen, oxygen and sulfur atoms besides carbon atom(s), and includes, for example, pyrrolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, dioxolan, oxazolidine, thiazolidine, triazolidine and the like.

Suitable "acyl" includes acyl having 1 to 20 carbon atom(s), such as formyl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl and aralkyloxycarbonyl.

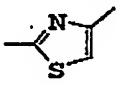
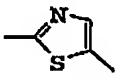
Suitable "alkylcarbonyl" includes alkylcarbonyl wherein the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C_1-C_6 alkyl of the above "lower alkyl"], such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and heptanoyl, in which more preferred one is C_1-C_4 alkyl-carbonyl.

Suitable "arylcarbonyl" includes arylcarbonyl wherein the aryl moiety has 6 to 10 carbon atom(s) [i.e. the aryl moiety is C_6-C_{10} aryl of the above "aryl"], such as benzoyl and naphthoyl.

Suitable "alkoxycarbonyl" includes alkoxycarbonyl wherein the alkoxy moiety has 1 to 6 carbon atom(s), such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl and hexyloxycarbonyl, in which more preferred one is alkoxycarbonyl wherein the alkoxy moiety has 1 to 4 carbon atom(s).

Suitable "aralkyloxycarbonyl" includes aralkyloxycarbonyl wherein the aryl moiety has 6 to 10 carbon atom(s) [i.e. the aryl moiety is C_6-C_{10} aryl of the above "aryl"] and the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C_1-C_6 alkyl of the above "lower alkyl"], such as benzyloxycarbonyl, phenethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl and 5-phenylpentyloxycarbonyl.

Suitable "bivalent residue derived from thiazole" of the "bivalent residue derived from optionally substituted thiazole" includes

 and  .

The "thiazole" may have 1 to 3 substituent(s) and the substitution sites are not particularly limited.

Suitable "substituent" of the above "optionally substituted thiazole" includes, for example,

(1) halogen which is as defined above;

(2) alkoxycarbonyl which is as defined above, such as ethoxycarbonyl;

(3) optionally substituted aryl, which aryl is as defined above and the substitution sites are not particularly limited, such as phenyl and 4-(methylsulfonyl)phenyl;

(4) a group of the formula: $-CONR^aR^b$ wherein R^a is hydrogen, lower alkyl, aryl or aralkyl and R^b is hydrogen, lower alkyl, aryl or aralkyl, wherein the lower alkyl, aryl and aralkyl are as defined above, such as N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl and N-benzylaminocarbonyl;

(5) a group of the formula: $-CONH-(CH_2)_k$-aryl wherein k is an integer of 0 to 6; the aryl is as defined

above, which may have 1 to 5 substituent(s) selected from the group consisting of $-NO_2$, $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above, $-CF_3$ and -O-aryl wherein the aryl is as defined above, and the substitution sites are not particularly limited;

(6) a group of the formula: $-CONH-(CH_2)_m$-heterocycle wherein m is an integer of 0 to 6; the heterocycle is as defined above, such as pyridine;

(7) a group of the formula: -CO-heterocycle wherein the heterocycle is as defined above, such as pyrrolidine, piperidine, piperazine, thiomorpholine, which may have 1 to 5 substituent(s) selected from the group consisting of -CO-(lower alkyl) wherein the lower alkyl is as defined above, -CO-O-(lower alkyl) wherein the lower alkyl is as defined above, $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above, oxo (i.e. =O) and a group of the formula: $-CONR^cR^d$ wherein R^c is hydrogen, lower alkyl, aryl or aralkyl and R^d is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(8) a group of the formula: $-(CH_2)_n$-aryl wherein n is an integer of 1 to 6; the aryl is as defined above, which may have 1 to 5 substituent(s) selected from the group consisting of -S-(lower alkyl) wherein the lower alkyl is as defined above, $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above, $-CO_2-$(lower alkyl) wherein the lower alkyl is as defined above, -NHCO-O-(lower alkyl) wherein the lower alkyl is as defined above and a group of the formula: $-CONR^eR^f$ wherein R^e is hydrogen, lower alkyl, aryl or aralkyl and R^f is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not

particularly limited;

(9) a group of the formula: $-(CH_2)_o$-heterocycle wherein o is an integer of 0 to 6; the heterocycle is as defined above, such as pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, which may have 1 to 5 substituent(s) selected from the group consisting of oxo (i.e. =O); -CO-(lower alkyl) wherein the lower alkyl is as defined above; -CO-O-(lower alkyl) wherein the lower alkyl is as defined above; $-SO_2$-(lower alkyl) wherein the lower alkyl is as defined above; -CO-(heterocycle) wherein the heterocycle is as defined above such as pyrrolidine, piperazine and morpholine, which may have 1 to 5 substituent(s) selected from the group consisting of lower alkyl and halogen, wherein the lower alkyl and halogen are as defined above, and the substitution sites are not particularly limited; and a group of the formula: $-CONR^gR^h$ wherein R^g is hydrogen, lower alkyl, aryl or aralkyl and R^h is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(10) a group of the formula: $-(CH_2)_p-NR^iR^j$ wherein p is an integer of 0 to 6; R^i is hydrogen, acyl, lower alkyl, aryl or aralkyl and R^j is hydrogen, acyl, lower alkyl, aryl or aralkyl wherein the acyl, lower alkyl, aryl and aralkyl are as defined above, and the lower alkyl may have 1 to 5 substituent(s) selected from the group consisting of a group of the formula: $-CONR^kR^l$ wherein R^k is hydrogen, lower alkyl, aryl or aralkyl and R^l is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(11) a group of the formula: -CON(H or lower alkyl)-$(CHR^m)_q$-T

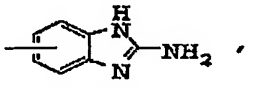
wherein q is an integer of 0 to 6; the lower alkyl is as defined above; R^m is hydrogen, aralkyl which is as defined above, or alkyl which is as defined above, which may be substituted by 1 to 3 substituent(s) selected from the group consisting of -OH and $-CONH_2$ and the substitution sites are not particularly limited; and T is hydrogen; a group of the formula: $-CONR^nR^o$ wherein R^n is hydrogen, lower alkyl, aryl or aralkyl and R^o is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above; $-NH-CO-R^p$ wherein R^p is lower alkyl which is as defined above or aralkyl which is as defined above; $-NH-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above; $-SO_2-$(lower alkyl) wherein the lower alkyl is as defined above; -heterocycle wherein the heterocycle is as defined above, such as pyridine, pyrrolidine and morpholine, which may have 1 to 3 substituent(s) such as oxo (i.e. =O), and the substitution sites are not particularly limited; or -CO-(heterocycle) wherein the heterocycle is as defined above, such as piperidine and morpholine; and

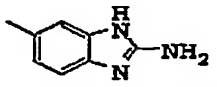
(12) a group of the formula: $-(CH_2)_r-CO-NR^tR^u$ wherein r is an integer of 1 to 6; R^t is hydrogen, lower alkyl, aryl or aralkyl and R^u is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above.

The substitution site on the aryl or heterocycle is any suitable position thereof, but not particularly limited.

Preferable "substituent" of the above "optionally substituted thiazole" is methylsulfonylbenzyl.

The substitution sites of R^2 on the phenyl in Compound (I) is not particularly limited.

When Z is a group of the formula:  , the substitution sites on the group are not particularly

limited.  is particularly preferable.

Any nitrogen atom in the amino (i.e. $-NH_2$), imino (i.e. =NH or -NH-) or the like contained in Compound (I) may be protected according to the methods, which are known to those skilled in the art, such as the methods described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like.

When Compound (I) has an asymmetric carbon atom in the structure, those skilled in the art will recognize that Compound (I) includes all stereoisomers.

Of the above-mentioned compounds, preferred are Compound (I), more preferably,
N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (see Structure 1),
N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (see Structure 46),
N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (see Structure 48),
N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (see Structure 56), and
N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (see Structure 107), particularly
N-{4-[2-(4-{[amino(imino)methyl]amino}-phenyl)ethyl]-1,3-thiazol-2-yl}acetamide and derivatives thereof.

The term "derivative" is intended to include all compounds derived from the original compound.

The pharmaceutically acceptable salt of Compound (I) of the present invention is nontoxic and a pharmaceutically acceptable conventional salt, which is exemplified by salts with inorganic or organic base such as alkali metal salt (e.g.,

sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

The Compound (I) can be also formulated as a pharmaceutically acceptable acid addition salt. Examples of the pharmaceutically acceptable acid addition salts for use in the pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, hydriodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and arylsulfonic acids, for example, p-toluenesulfonic acid.

As a pharmaceutically acceptable salt of Compound (I) represented by the formula (I), a pharmaceutically acceptable acid addition salt such as (mono-, di- or tri-)hydrochloride and hydriodide, particuraly hydrochloride, is preferable.

The above-mentioned Compound (I) may be commercially available or can be produced based on a known reference.

The composition can be administered in accordance with the present inventive method by any suitable route. Suitable routes of administration include systemic, such as orally or by injection, topical, periocular (e.g., subTenon's), subconjunctival, intraocular, intravitreal, intracameral, subretinal, suprachoroidal and retrobulbar administrations. The manner in which the VAP-1 inhibitor is administered is dependent, in part, upon whether the treatment of a VAP-1 associated disease is prophylactic or therapeutic.

The composition is preferably administered as soon as possible after it has been determined that a subject such as mammal, specifically a human, is at risk for a VAP-1 associated disease (prophylactic treatments) or has begun to develop a VAP-1 associated disease (therapeutic treatments).

Treatment will depend, in part, upon the particular VAP-1 inhibitor to be used, the amount of the VAP-1 inhibitor to be administered, the route of administration, and the cause and extent, if any, of a VAP-1 associated disease realized.

One skilled in the art will appreciate that suitable methods of administering a VAP-1 inhibitor, which is useful in the present inventive method, are available. Although more than one route can be used to administer a particular VAP-1 inhibitor, a particular route can provide a more immediate and more effective reaction than another route. Accordingly, the described routes of administration are merely exemplary and are in no way limiting.

The dose of the composition administered to the administration subject such as animal including human, particularly a human, in accordance with the present invention should be sufficient to effect the desired response in the subject over a reasonable time frame. One skilled in the art will recognize that dosage will depend upon a variety of factors, including the strength of the particular VAP-1 inhibitor to be employed, the age, species, conditions or disease states, and body weight of the subject, as well as the degree of a VAP-1 associated disease. The size of the dose also will be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular VAP-1 inhibitor and the desired physiological effect. It will be appreciated by one of ordinary skill in the art that various conditions or disease states may require prolonged treatment involving multiple administrations.

Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated

with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached.

Generally, the compound (I) can be administered in the dose of from about 1 μg/kg/day to about 300 mg/kg/day, preferably from about 0.1 mg/kg/day to about 10 mg/kg/day, which is given in a single dose or 2 to 4 doses a day or in a sustained manner.

本発明における水性製剤とは、Compound (I)で示されるチアゾール誘導体が水に溶解した澄明な水溶液の製剤を意味し、点眼剤、点鼻剤、点耳剤、吸入剤、噴霧剤、内服液剤、注射剤（静脈内注射、動脈内注射、皮下注射、筋肉内注射、腹腔内注射、眼内注射等）などの形態で使用することができる。本発明のチアゾール誘導体を含む水性製剤では、使用される添加剤（例えば、塩化ナトリウムなど）によっては、著しくチアゾール誘導体の溶解度が低下し、結晶が析出するなど、安定で長期保存可能な水性製剤を得ることができないという問題点があったが、本発明に用いる添加剤であるポリオール、糖、糖アルコール、および/またはホウ酸あるいはその塩を含む水性製剤は、チアゾール誘導体の溶解度に悪影響を与えることなく、安定で長期保存可能な水性製剤を得ることを可能とする。

本発明に用いられる添加剤としては、グリセリン、ポリエチレングリコール、プロピレングリコール、ポリビニルアルコールなどのポリオール；ブドウ糖、ソルビトール、マンニトール、キシリトールなどの糖または糖アルコール；ホウ酸あるいはその塩があげられる。この添加剤は、必要あるいは目的に応じて2種以上を組み合わせて使用してもよい。特に好ましい添加剤は、グリセリン、マンニトール、ホウ酸あるいはその塩である。

本発明に用いられる添加剤の濃度は、チアゾール誘導体の種類や濃度、あるいは添加物の種類や分子量によっても異なるが、通常、組成物全体に対して０．００１～１０w/v%程度、好ましくは０．０１から５w/v%程度である。

本発明の水性製剤は、必要に応じ、また本発明の目的、すなわちチアゾール誘導体の溶解度に実質的に影響しない限りにおいて、通常、製剤学的に使用される緩衝剤、保存剤、安定化剤、増粘剤などの他の添加剤を加えてもよい。チアゾール誘導体の溶解度に実質的に影響しない点から塩化ベンザルコニウム、クロロブタノール、パラオキシ安息香酸エステルなどの保存剤や、ポビドン、メチルセル

ロースなどの増粘剤などが好ましいものとしてあげられる。

The present inventive method also can involve the co-administration of other pharmaceutically active compounds. By "co-administration" is meant administration before, concurrently with, e.g., in combination with the VAP-1 inhibitor in the same formulation or in separate formulations, or after administration of a VAP-1 inhibitor as described above. For example, corticosteroids, prednisone, methylprednisolone, dexamethasone, or triamcinolone acetinide, or noncorticosteroid anti-inflammatory compounds, such as ibuprofen or flubiprofen, can be co-administered. Similarly, vitamins and minerals, e.g., zinc, anti-oxidants, e.g., carotenoids (such as a xanthophyll carotenoid like zeaxanthin or lutein), and micronutrients can be co-administered.

In addition, the composition according to the present invention is useful for preparing a medicament such as a therapeutic or prophylactic agent for the VAP-1 associated diseases.

The compound (I) according to the present invention are listed in the following tables.

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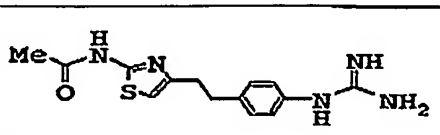
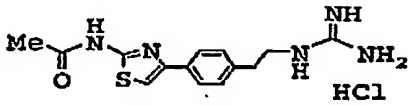
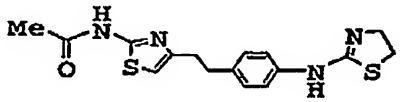
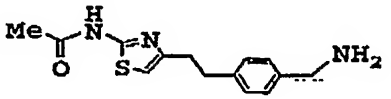
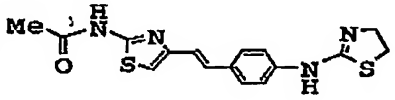
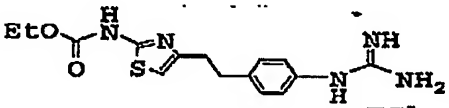
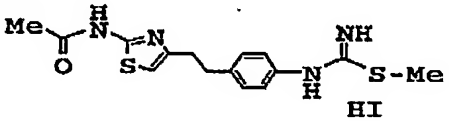
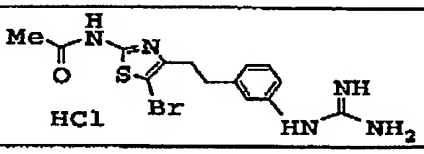
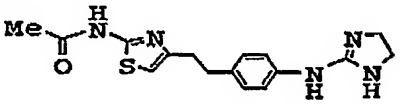
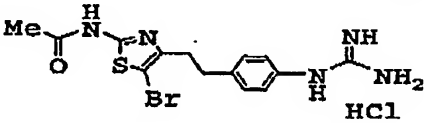
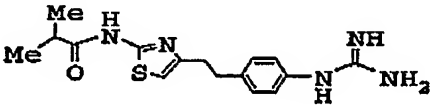
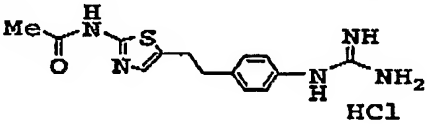
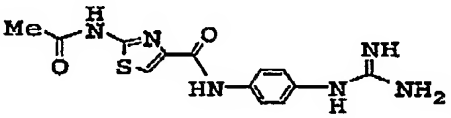
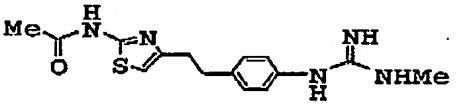
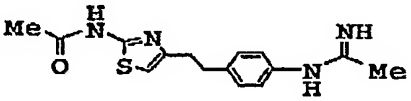
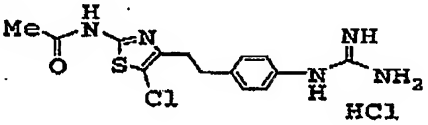
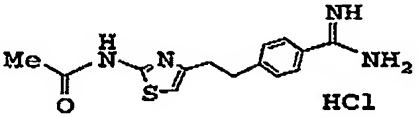
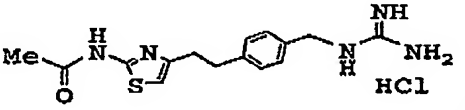
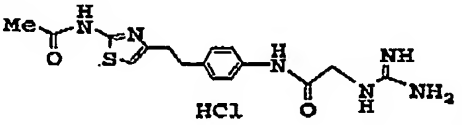
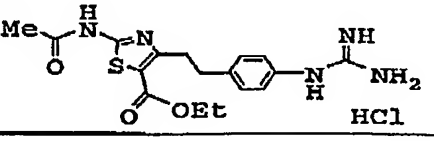
1		11	
2		12	
3		13	
4		14	
5		15	
6		16	
7		17	
8		18	
9		19	
10		20	

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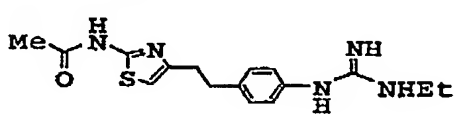
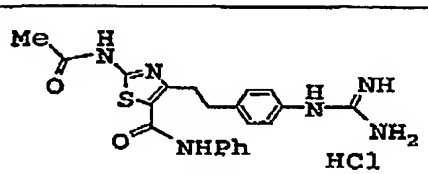
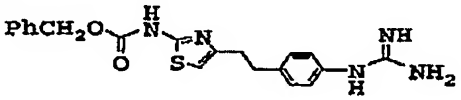
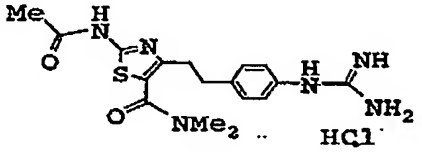
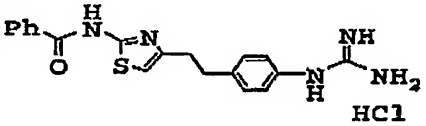
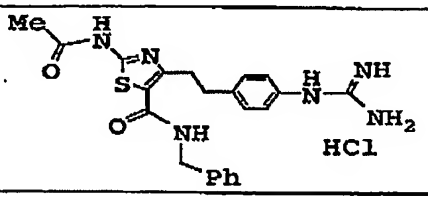
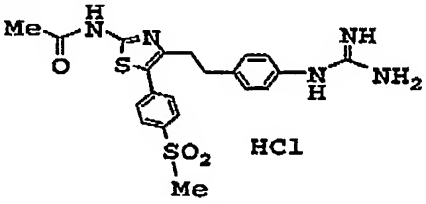
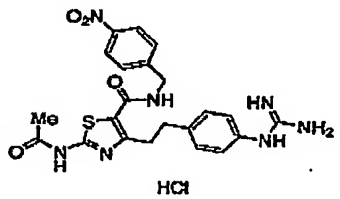
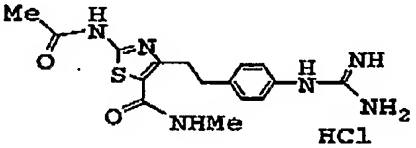
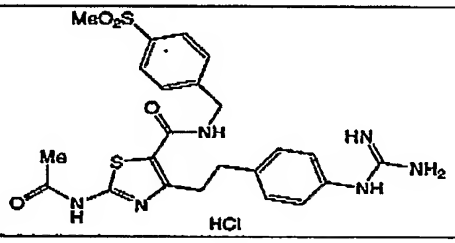
21		26	
22		27	
23		28	
24		29	
25		30	

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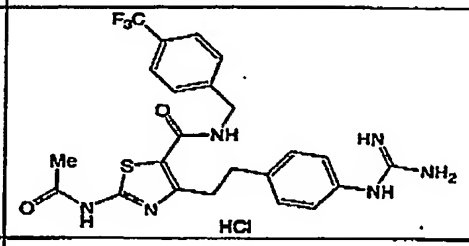
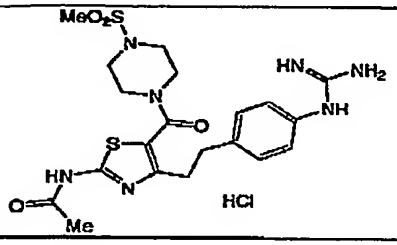
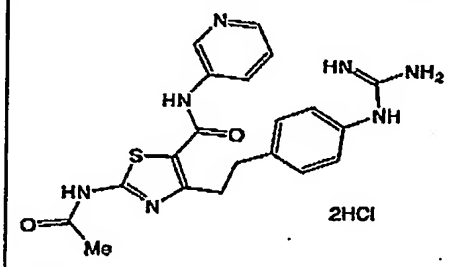
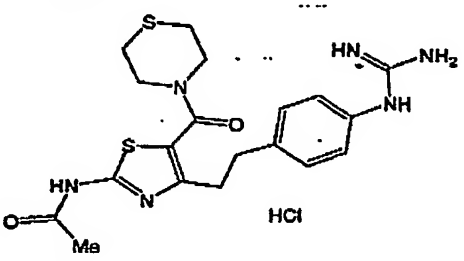
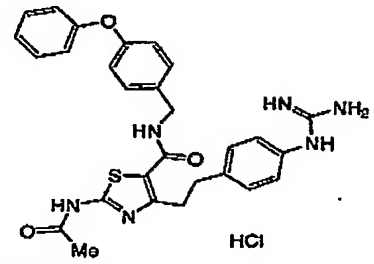
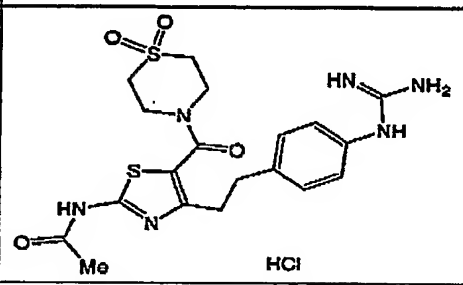
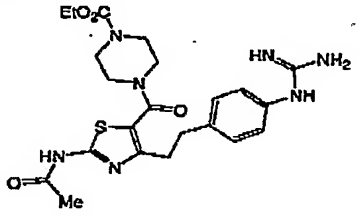
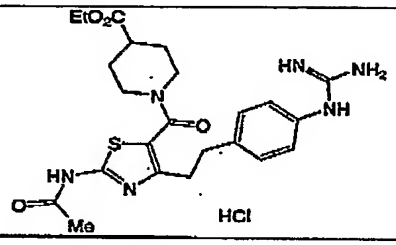
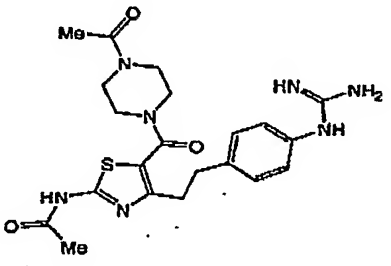
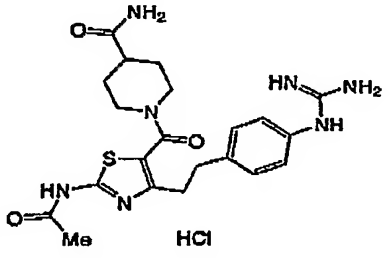
31		36	
32		37	
33		38	
34		39	
35		40	

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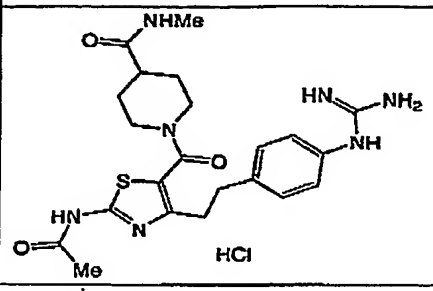
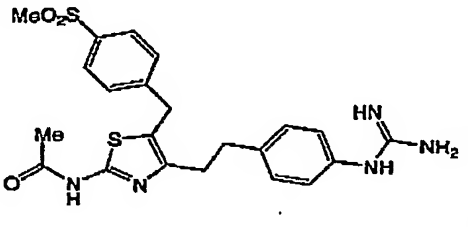
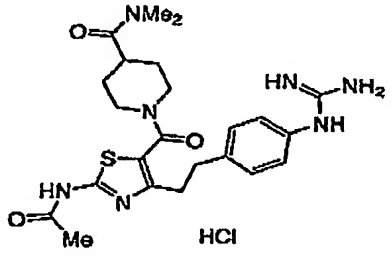
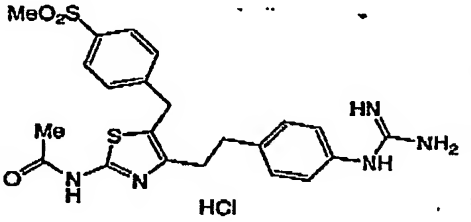
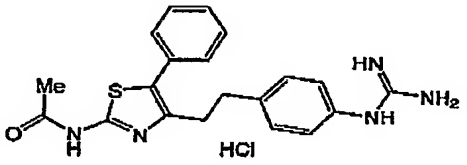
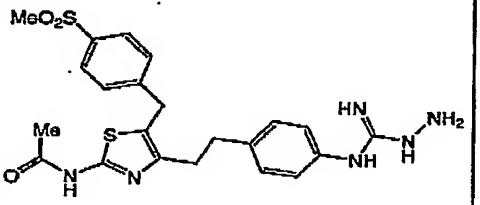
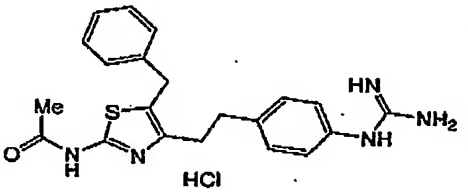
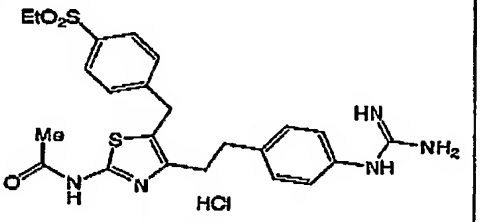
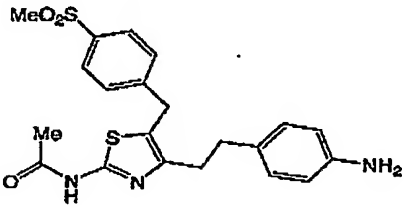
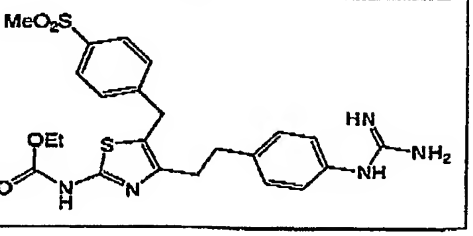
41		46	
42		47	
43		48	
44		49	
45		50	

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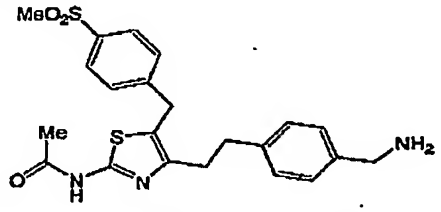
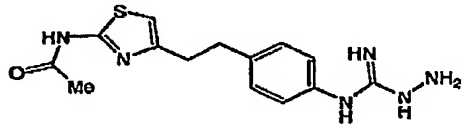
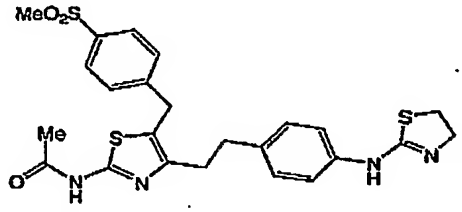
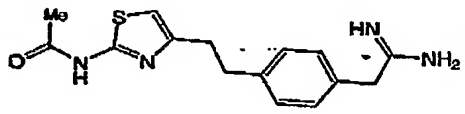
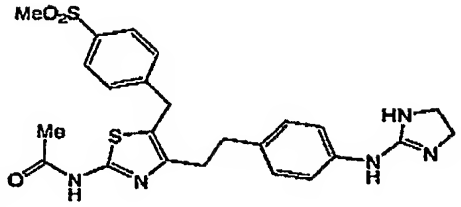
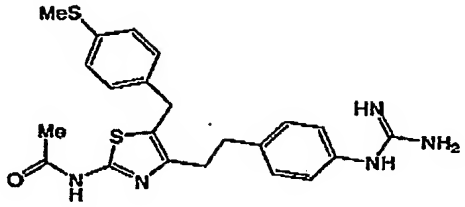
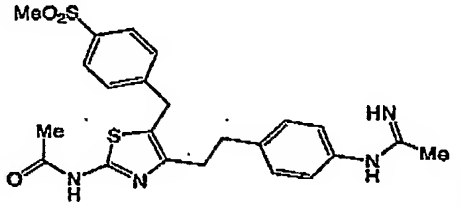
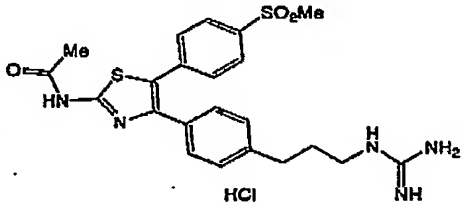
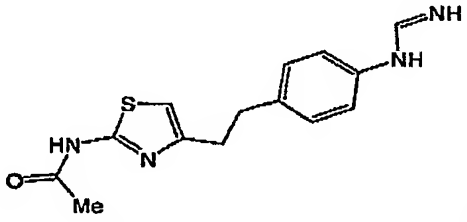
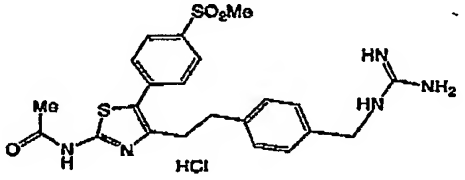
51		56	
52		57	
53		58	
54		59	
55		60	

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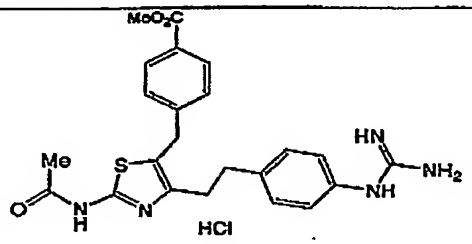
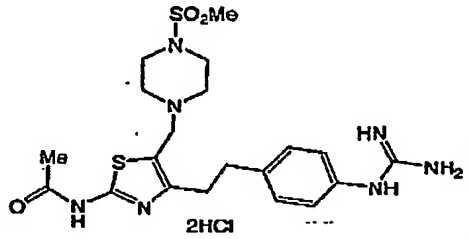
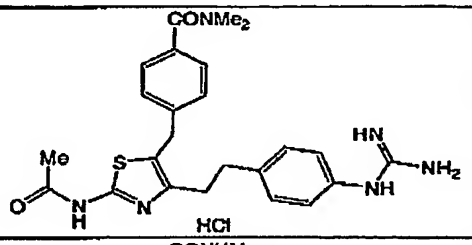
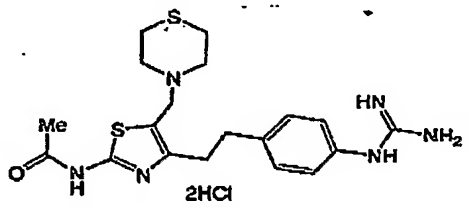
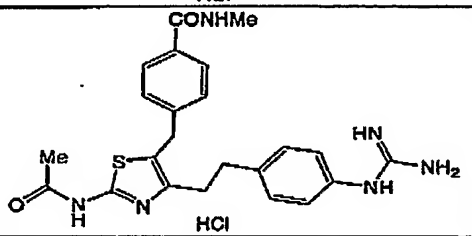
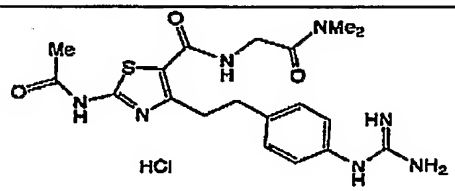
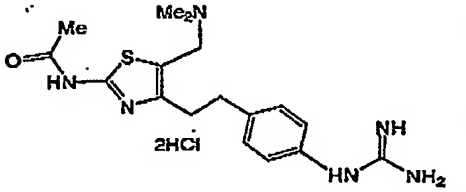
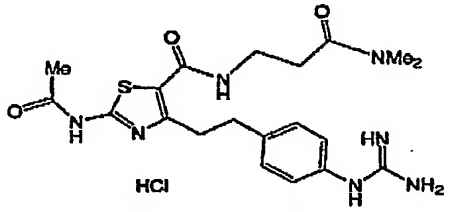
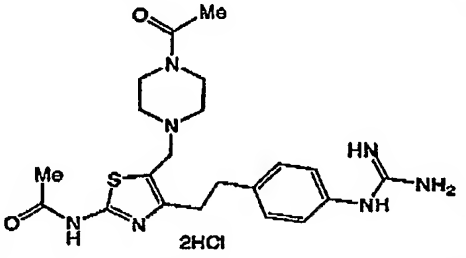
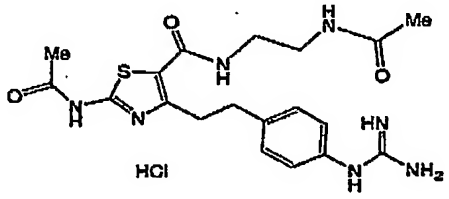
61		66	
62		67	
63		68	
64		69	
65		70	

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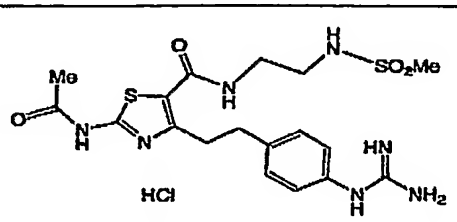
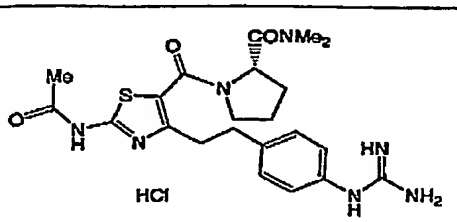
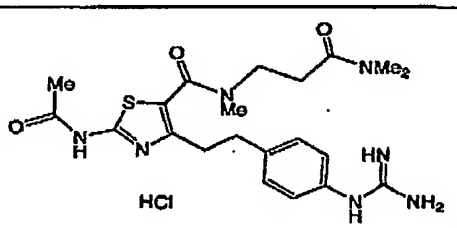
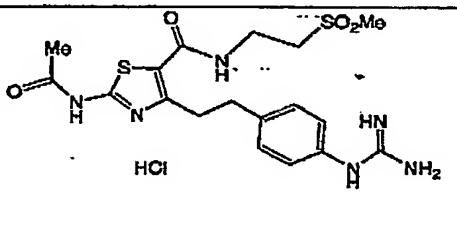
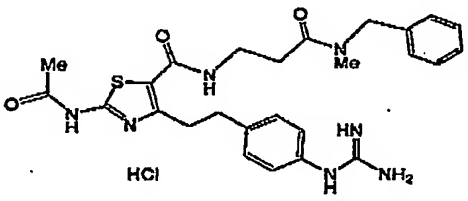
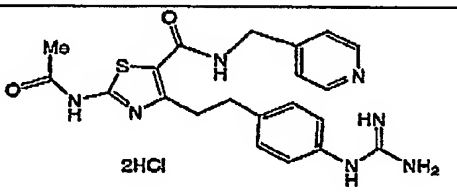
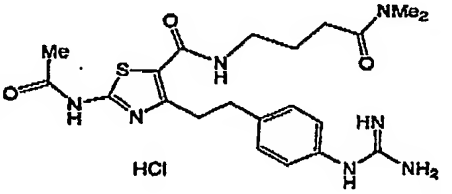
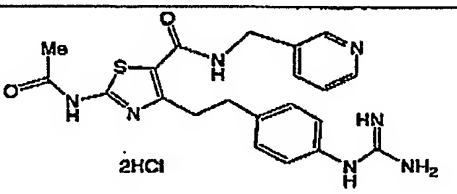
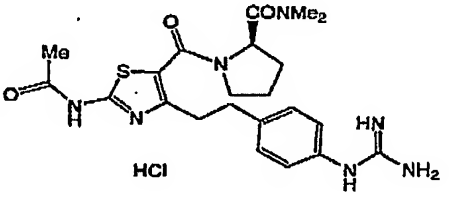
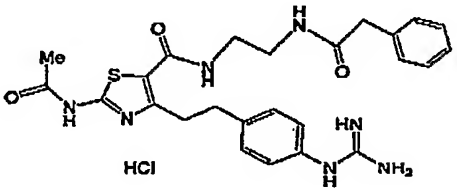
71		76	
72		77	
73		78	
74		79	
75		80	

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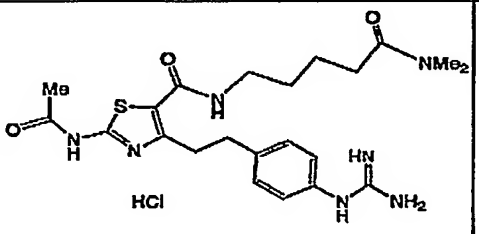
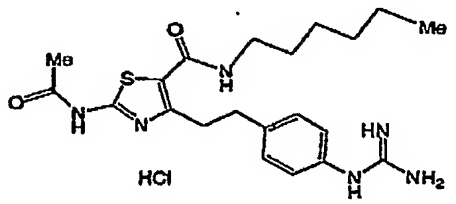
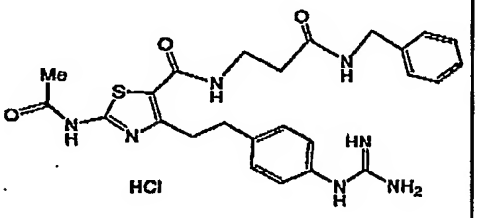
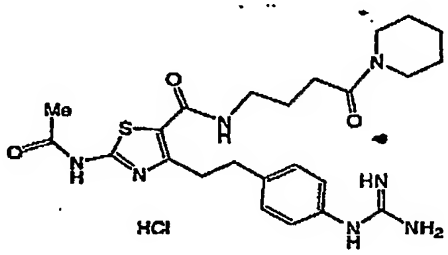
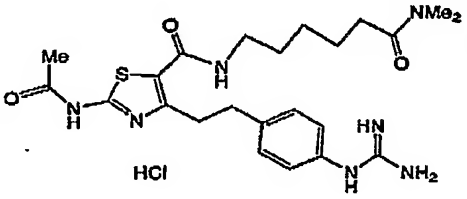
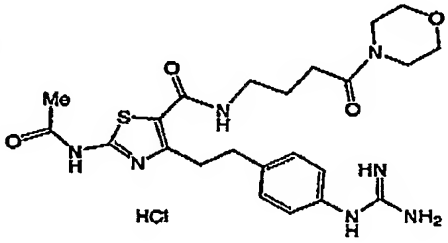
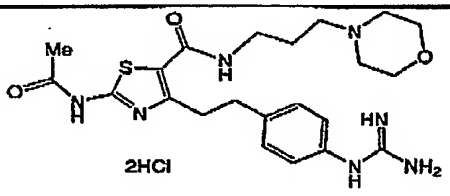
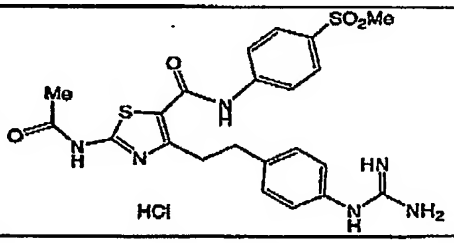
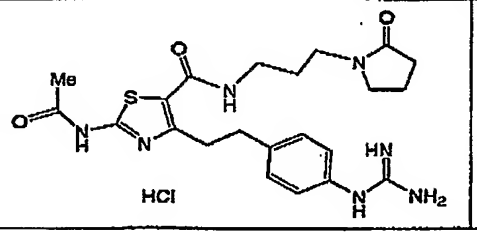
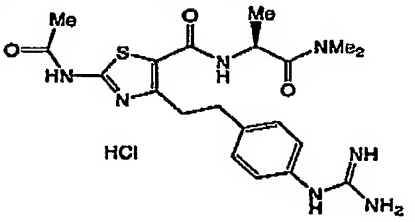
81		86	
82		87	
83		88	
84		89	
85		90	

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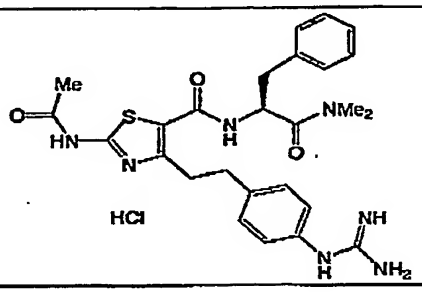
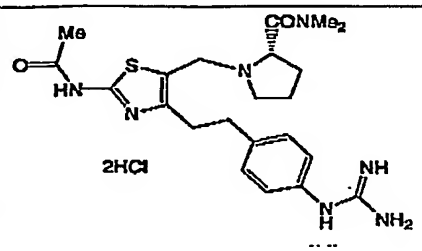
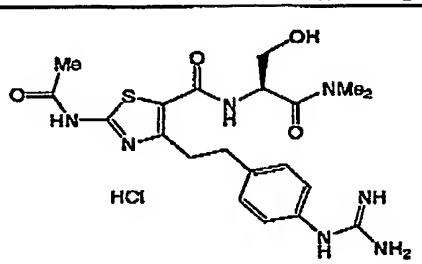
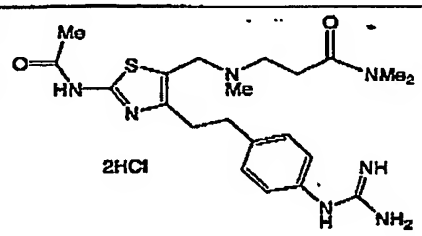
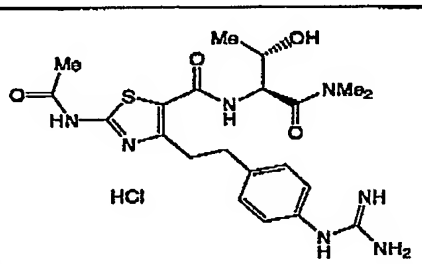
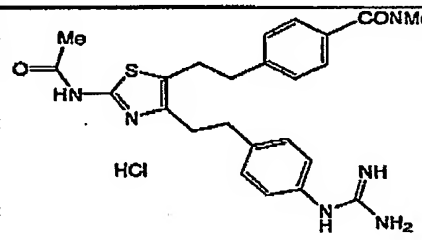
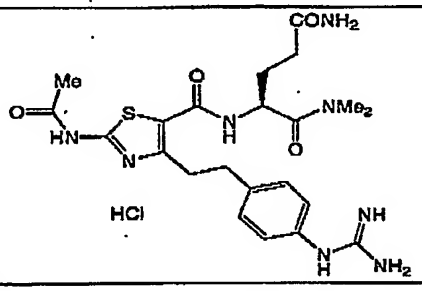
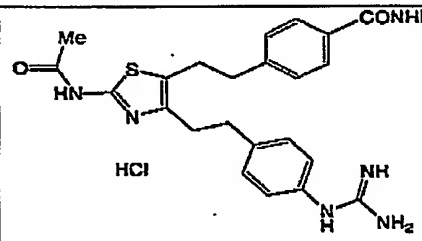
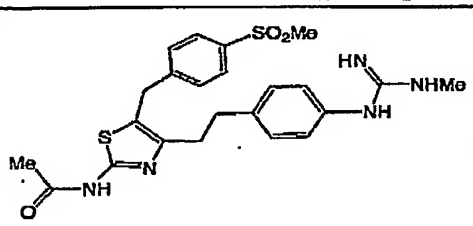
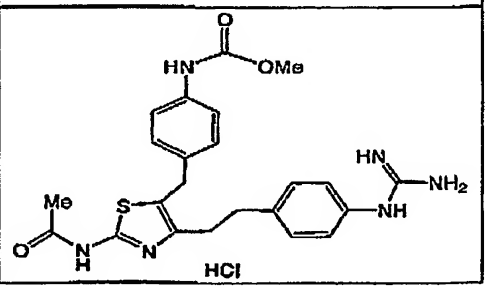
91		96	
92		97	
93		98	
94		99	
95		100	

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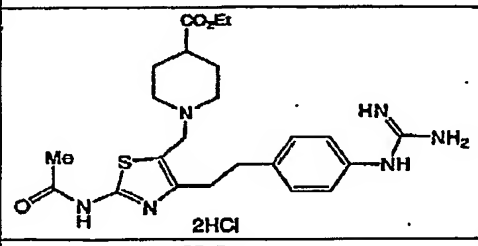
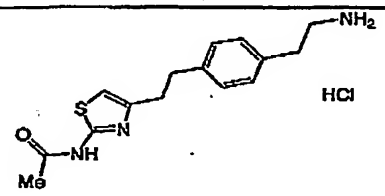
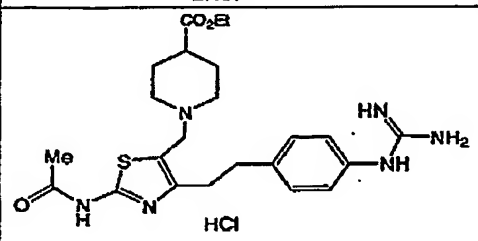
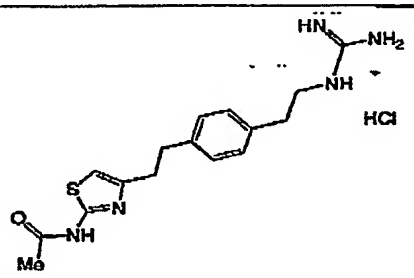
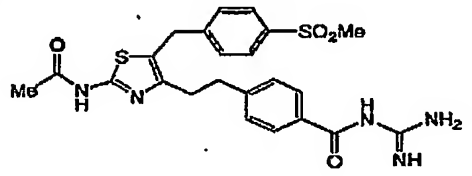
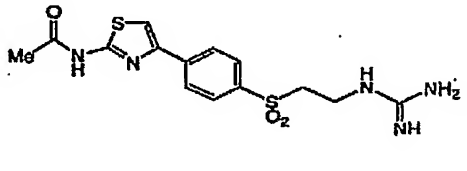
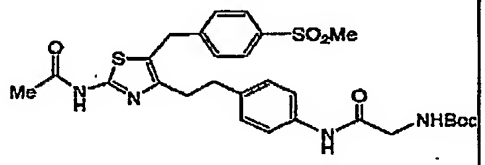
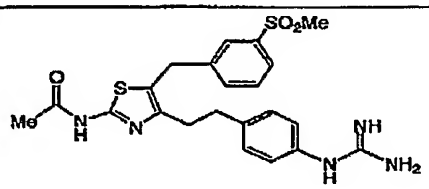
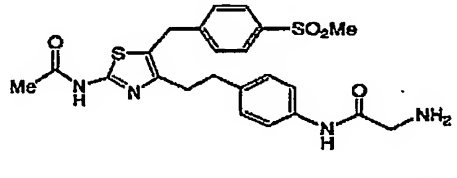
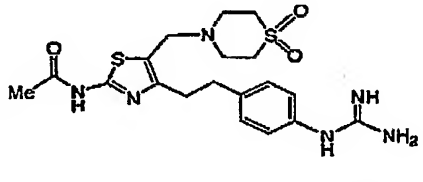
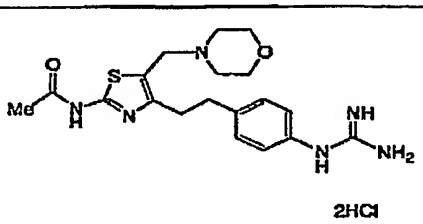
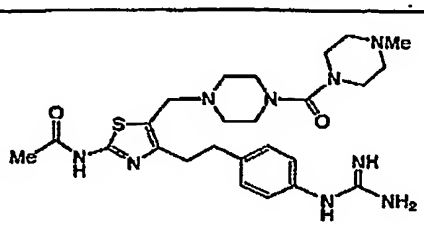
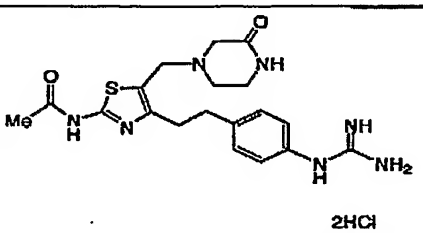
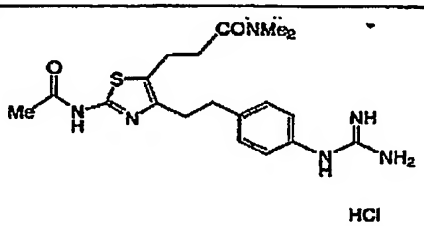
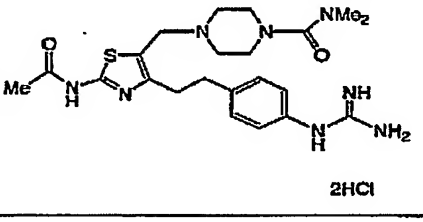
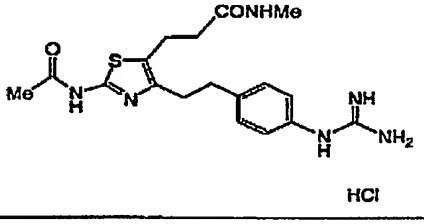
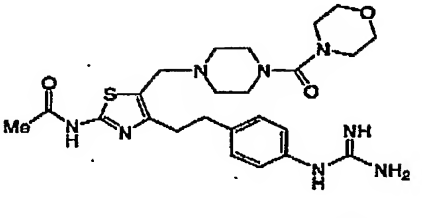
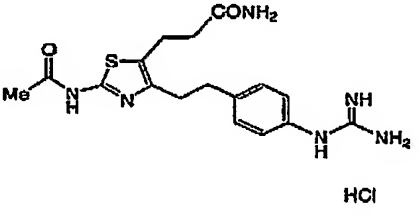
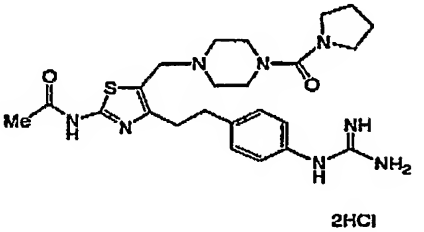
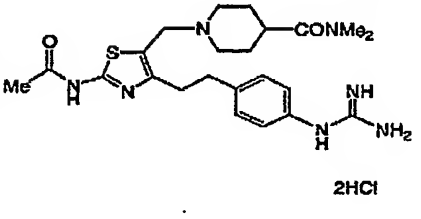
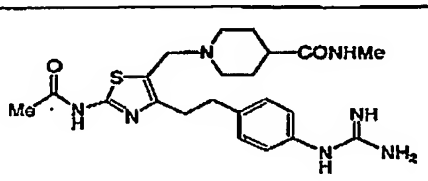
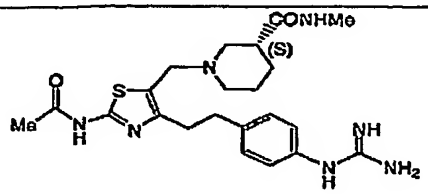
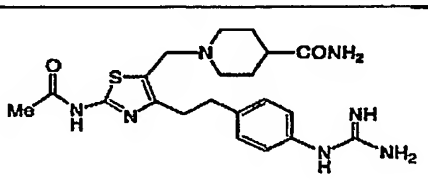
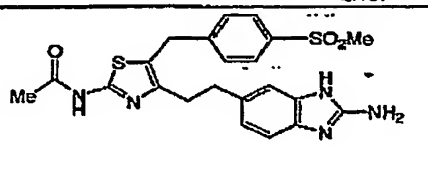
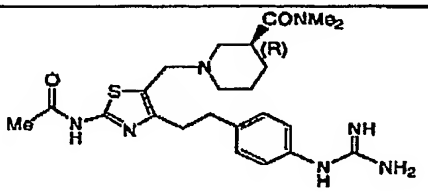
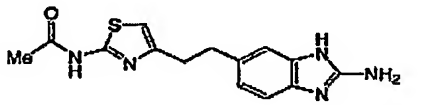
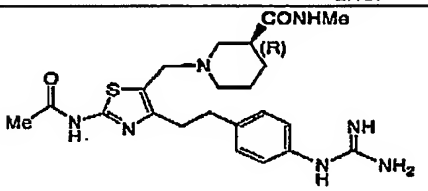
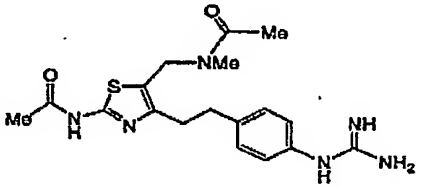
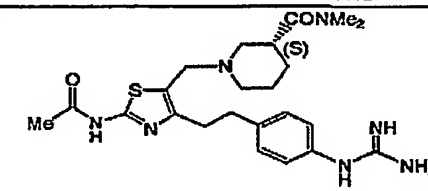
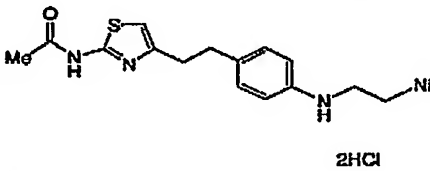
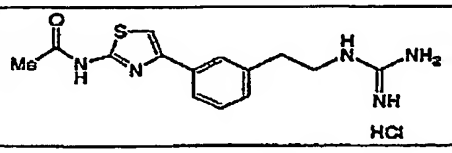
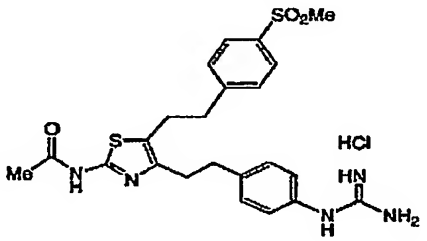
101	 2HCl	106	 HCl
102	 HCl	107	 HCl
103		108	 HCl
104		109	 HCl
105	 HCl	110	 2HCl

No.	Structure	No.	Structure
111	 2HCl	116	 3HCl
112	 2HCl	117	 HCl
113	 2HCl	118	 HCl
114	 2HCl	119	 HCl
115	 2HCl	120	 2HCl

No.	Structure	No.	Structure
121	 2HCl	126	 2HCl
122	 2HCl	127	
123	 2HCl	128	
124	 2HCl	129	 HCl
125	 2HCl	130	 2HCl

No.	Structure
131	
132	

以下、本発明を実施例により、さらに詳細に説明するが、これは本発明を限定するものではない。

実施例

試験例１

化合物１に注射用蒸留水を加えて撹拌し、約pH7の飽和溶液（3.55 mg/mL）を調製した。

化合物２に注射用蒸留水を加え、塩酸を加えながら撹拌し、約pH3の飽和溶液（1.12 mg/mL）を調製した。

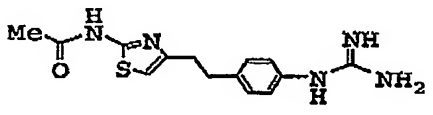
化合物３に注射用蒸留水を加え、塩酸を加えながら撹拌し、約pH7の飽和溶液（10.73 mg/mL）を調製した。

調製した化合物１、２、３の飽和溶液に0.4%相当量の塩化ナトリウムを加えて撹拌し、析出の有無、溶解度の変化（上清の濃度変化）を調べた。同様に0.85%相当量の塩化ナトリウムを加えて撹拌し、析出の有無、溶解度の変化（上清の濃度変化）を調べた。

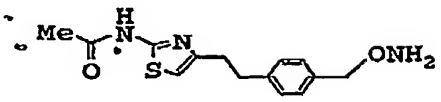
表１．試験例１の結果（化合物１、２、３の塩化ナトリウムによる溶解度への影響）

化合物名	添加した塩化ナトリウム量（%）	性状（析出の有無）	溶解度（mg/mL）	対添加前濃度（%）
化合物１	0	なし	3.55	≒100
	0.4	あり	1.11	31
	0.85	あり	0.69	20
化合物２	0	なし	1.12	≒100
	0.4	なし	1.17	100
	0.85	なし	1.19	100
化合物３	0	なし	10.73	≒100
	0.4	あり	1.76	16
	0.85	あり	0.86	8

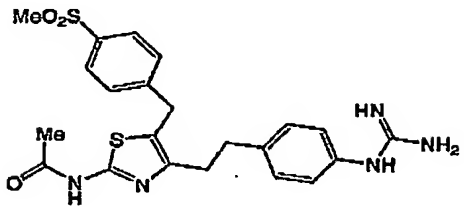
化合物１：



化合物２：



化合物３：



試験例２

試験例１と同様に調製した化合物３の飽和溶液に、２.５%相当量のグリセリンを加えて撹拌し、析出の有無、溶解度の変化（上清の濃度変化）を調べた。

同様に３.５%相当量のマンニトール、２%相当量のホウ酸、０.２%相当量の塩化カリウム、１%相当量のリン酸水素ナトリウム、１%相当量のクエン酸ナトリウムを加えて撹拌し、析出の有無、溶解度の変化（上清の濃度変化）を調べた。

表２．試験例２の結果（化合物３の溶解度に対する各添加剤の影響）

化合物３の飽和溶液に添加した添加剤及び添加量		性状（析出の有無）	添加前濃度（mg/mL）	添加後濃度（mg/mL）	対添加前濃度（%）
グリセリン	２.５%	なし	１１.５１	１０.９１	９５
マンニトール	３.５%	なし	１１.５１	１１.０５	９６
ホウ酸	２%	なし	１１.５１	１１.５９	１００
塩化カリウム	０.２%	あり	１０.７３	３.１６	２９
リン酸水素ナトリウム	１%	あり	１０.７３	２.５４	２４
クエン酸ナトリウム	１%	あり	１０.７３	０.４８	４

INDUSTRIAL APPLICABILITY

The present invention provides an aqueous composition comprising a thiazole derivative of the formula (I): $R^1-NH-X-Y-Z$ (I)

wherein each symbol is as defined above, or a parmaceutically acceptable salt thereof, and an additive selected from the group consisting of polyol, sugar, sugar alcohol, boric acid or its salt, and water.

本発明は特定のチアゾール誘導体にポリオール、糖、糖アルコール、ホウ酸あるいはその塩を配合することにより、チアゾール誘導体の溶解性を保持した安定な水性製剤を提供することが可能である。

CLAIMS

1. An aqueous composition comprising a thiazole derivative of the formula (I):

$$R^1—NH—X—Y—Z \quad (I)$$

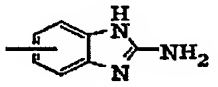
wherein

R^1 is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:

 or 

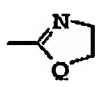
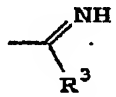
wherein R^2 is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or $-SO_2-$;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or $-CH_2NH-$, provided that when B is -CO- or -O-, D is not a bond; and

E is optionally protected amino, $-N=CH_2$,

 or 

wherein

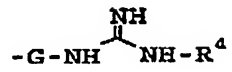
Q is -S- or -NH-; and

R^3 is hydrogen, lower alkyl, lower alkylthio or $-NH-R^4$ wherein R^4 is hydrogen, $-NH_2$ or lower alkyl;

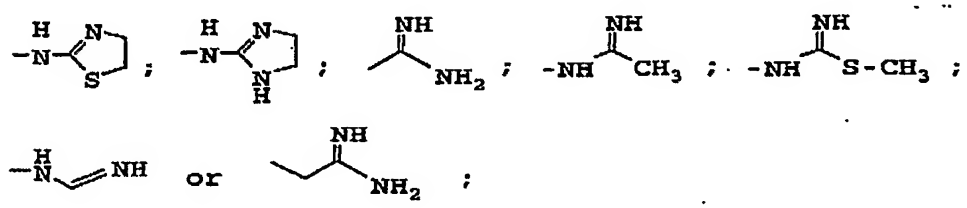
or a pharmaceutically acceptable salt thereof, and an additive selected from the group consisting of polyol, sugar, sugar alcohol, boric acid or its salt, and water.

2. The composition of claim 1, wherein Z of the formula (I) is a group of the formula:

wherein R^2 is a group of the formula:

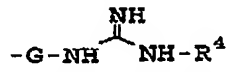


(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen, $-NH_2$ or lower alkyl); $-NH_2$; $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;

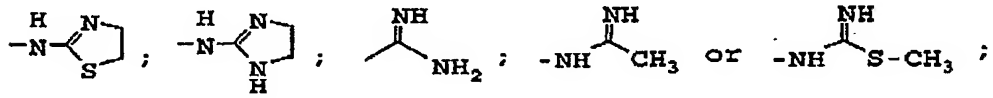


or a pharmaceutically acceptable salt thereof.

3. The composition of claim 2, wherein R^2 of the formula (I) is a group of the formula:



(wherein G is a bond, $-NHCOCH_2-$ or lower alkylene and R^4 is hydrogen or lower alkyl); $-CH_2NH_2$; $-CH_2ONH_2$; $-CH_2ON=CH_2$;



or a pharmaceutically acceptable salt thereof.

4. The composition of any of claims 1 to 3, wherein R^1 of the formula (I) is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl, or a pharmaceutically acceptable salt thereof.

5. The composition of claim 1, wherein the tiazole derivative is

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide,

or a pharmaceutically acceptable salt thereof.

ABSTRACT

The present invention provides an aqueous composition comprising a thiazole derivative of the formula (I): R^1—NH—X—Y—Z (I)

wherein each symbol is as defined above, or a parmaceutically acceptable salt thereof, and an additive selected from the group consisting of polyol, sugar, sugar alcohol, boric acid or its salt, and water.

本発明は特定のチアゾール誘導体にポリオール、糖、糖アルコール、ホウ酸あるいはその塩を配合することにより、チアゾール誘導体の溶解性を保持した安定な水性製剤を提供することが可能である。